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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/467,076	12/20/1999	JOSE CIBELLI	000270-088	1896

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EXAMINER

WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 04/21/2004

*21*

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/467,076

Applicant(s)

CIBELLI ET AL.

Examiner

Joseph T. Voitach

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 21 July 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-34 and 36-58 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-34, 36-58 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on July 21, 2003 has been entered.

**DETAILED ACTION**

This application filed December 20, 1999 which claims benefit to PCT/US99/04608, filed March 2, 1999, which claims priority to 08/699,040, filed August 19, 1996, and is a continuation in part of 09/395,368, filed September 14, 1999, now abandoned, which is a continuation in part of 09/260,468, filed March 2, 1999, which are a continuation in part of 09/032,945, filed March 2, 1998, now abandoned, which is a continuation in part of 08/699,040, filed August 19, 1996.

As requested in Applicants' request for continued examination Applicants' amendment filed December 26, 2002 has been entered. The specification has been amended. Claims 1, 5-8, 10-16, 18, 19, 24, 25, 27-34, 38, 50 and 56-58 have been amended. Claims 1-34 and 36-58 are pending and currently under examination.

***Specification***

The objection to the specification because the reference to related applications should be updated to reflect the status of the applications is withdrawn.

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The amendment to the specification has obviated the basis of the objection.

### *Claim Objections*

Claims 27-33 and 57 objected to because the claims should begin with an article such as "A", "The", etc. (see MPEP § 608.01(m)) is withdrawn.

The amendment to the claims has obviated the objection.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-34, 36-58 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn.

Applicants summarize the basis of the rejection note that the instantly claimed cells and methods of making are distinguished from those disclosed in the prior art because the cells contain xenogeneic mitochondria (see also discussion regarding art rejections). More specifically, Applicants argue that the *Bos Taurus* and *Bos gaurus* are distinct and different species of the genus *Bos* as evidenced by the number of chromosomes and art recognized taxonomy of *Bos* (page 8 and

supporting information in appendix). See Applicants' amendment pages 7-8. Applicants arguments have been fully considered, and found persuasive in part.

In view of the amendment to the claims and Applicants' arguments are found persuasive. Specifically, the claims now encompass the exchange of nuclear material and mitochondria between ungulates. The art supports that basis of a rejection of non-enablement for species that are distantly related and some species that are not so distantly related, more specifically as it is related to the ability of one species mtDNA to complement the nuclear material of another species. However, the evidence of record indicates that at least two species/subspecies of *Bos* have been successfully used to generate cells and animals that have mtDNA and nuclear material from two different sources. It is noted that the claims are broad encompassing any ungulate, however there is no specific evidence of record that ungulates represent a groups of species so distantly related that their mtDNA will not complement the nuclear material of one another. The information regarding mouse species suggest that for some species that this may be the case, however this is not apparent for at least the species of *Bos* (as noted in the basis of the prior rejection Meirelles *et al.* using *Mus caroli* and *Mus musculus* and citing Dominko *et al.* conclude that in light of their results and the failures of the prior art, that nuclear transfer across subspecies barriers is possible, and early experiments demonstrate that the methodology of nuclear transfer can be performed, however the cells resulting from cross species nuclear transfer demonstrate dramatically decreased proliferation capacity the greater the phylogenetic distance, and have been incapable of fully developing/proliferating (see for example Prather *et al.* (J Reprod Fertil Suppl 41:125-34, 1990)). Based on the evidence of record, Applicants arguments have been found persuasive. Post filing art provides evidence that appears that species of *Bos* will complement each other resulting in a viable cell and even an intact animal.

Further, while ungulates represent a large number of animals, it would not constitute an undue burden to test different nuclear donors with different recipient oocytes to determine if even initially a viable culturable cell will result.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-34, 36-49 and 55-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the claims are vague, unclear and confusing because while the preamble indicates that the method is used for producing ES cells with the mitochondria of one species and the nuclear material of second different species, the final step simply recites isolating cells.

Applicants argue that the method is set forth in clear and precise terms, and accords with the written description of the invention provided in the specification (bridging pages 8-9). Applicants summarize the basis of the rejection and the claims as amended and argue that the claims are definite. See Applicants' amendment, pages 8-9. Applicants' arguments have been fully considered, but not found persuasive.

As indicated in the prior office action, there is no indication in the final step that the cells isolated are chimeric and meet the limitation recited in the preamble. Examiner would agree that the terms used in the method steps are defined, however the basis of the rejection focuses on the completeness of the claims and what results from practicing the method steps as set forth. As

discussed above in the section regarding 35 USC 112, first paragraph, as supported by the teachings in the present specification and the art of record, using nuclear transfer methodology results in only mtDNA homoplasmy. Practicing the method as claimed would result in cells that have only one source of mtDNA. In the case where the mtDNA is not compatible with the nuclear material used in nuclear transfer, there will be a selection of mtDNA that is complementary to the nuclear material when the cells are cultured and expanded. Non-complementary mtDNA will be lost, or if there is not enough complementary mtDNA to support the growth and culture of the resulting cells, the culture of cells will not be viable and not result in embryonic stem-like cells as required in the final step of the claims. The art of record and the specification teach that the initial presence of two sources of mtDNA, heteroplasmy, still results in cells which are homogeneous for one mtDNA, and the process appears random without some potential sort of selection.

The claims are unclear because it appears that the cells isolated in the final step of claim 1(vi) may be both chimeric or normal. Clearly indicating in the final step that the cells which are isolated have the nuclear material of one species and the mitochondria of a second different species, and that further method steps do not alter this outcome would obviate the basis of the rejection.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
- (c) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 27-32 rejected under 35 U.S.C. 102(a) as being anticipated by Granerus *et al.* is withdrawn.

Claims 27-34, 36 and 50-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Tsukamoto *et al.* is withdrawn.

Claims 27-34, 36 and 50-54 are rejected under 35 U.S.C. 102(e) as being anticipated by Yamane is withdrawn.

The amendment to the claims to clearly indicate that the resulting cells have nuclear materials and mitochondria from two different species has differentiated the claimed cells from that taught by cited references.

Claims 27-34, 36 and 50-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Robl *et al.* (WO 98/07841).

Robl *et al.* teach a method of nuclear transfer. Importantly, Robl *et al.* teach a method of nuclear transfer wherein the resulting cell is chimeric cell comprising an enucleated oocyte from one mammal which is a different species from that of the transferred nuclei. Upon review of the teachings in the present disclosure, the methodology required to practice the instantly claimed method is that known and commonly used in the art. The instant disclosure does not provide any new or unique methodology which would distinguish it from that previously described. Where, as



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here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product (*In re Ludtke*). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). In the instant case, the cells resulting from practicing the methods taught by Robl *et al.* would be the same as those instantly claimed.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-34, 36 and 50-54 rejected under 35 U.S.C. 103(a) as being unpatentable over Tsukamoto *et al.* (US Patent 5,716,827) is withdrawn.

Amendments to the claims to clearly indicate that the resulting cells have nuclear materials and mitochondria from two different species has differentiated the claimed cells from that taught by Tsukamoto *et al.* ('827).

Claims 1-34 and 36-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robl *et al.* (WO 98/07841) in view of Kenyon *et al.* (PNAS, 94:9131-9135, 1997).

Robl *et al.* teach a method of nuclear transfer wherein the resulting cell is chimeric cell comprising an enucleated oocyte from one mammal which is a different species from that of the transferred nuclei. At the time of filing Kenyon *et al.* teach that nuclear and mitochondrial genomes have coevolved and that there is a species specific compatibility for a mitochondria from one species to support viability and growth of a cell of second different species with respect to the nuclear material (see summary in abstract). Moreover, Kenyon *et al.* teaches that interspecies hybrid cells have been previously made and described in the art, including mouse and hamster, mouse and rat and mouse and human, and in each case the resulting cells have demonstrated that the mtDNA corresponded to the cognate nuclear material, i.e. the only viable functional cell that could result from such a interspecies fusion would be one wherein the nuclear and mitochondrial genomes were compatible (page 9133, discussion section). To this end, any viable hybrid cell in which cross species nuclear transfer was done and that was successfully cultured must have at the time of fusion or over time in culture obtained complementary mtDNA that was from the nuclear donor. Based on the evidence provided by Kenyon *et al.* cells without complementary mtDNA would not be viable in culture. Based on the knowledge in the art that previous interspecies cybrids demonstrated that the mtDNA corresponded to the cognate nuclear

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material (discussion section), and the specific results of Kenyon *et al.* that mtDNA of distant species would not be able to functionally complement the nuclear genome of another species, one of skill in the art would have been motivated to provide mtDNA from related species that functionally complement the nuclear donor. Based on the teaching of Kenyon *et al.* that functionally complimentary mtDNA is required to form a viable cybrid cell, and that the only viable cell previously made in the prior art had only cognate mitochondrial and nuclear DNA, it would have been obvious that in method of making embryonic stem cells with oocytes of different species than the nuclear donor through the use of nuclear transfer methodology to ensure that the resulting cybrid contained the appropriate mtDNA. Kenyon *et al.* teach that other hybrid cells have been made and each have mtDNA and nuclear DNA that is from the same species therefore, there would have been a reasonable expectation of success that providing an oocyte without mtDNA and providing donor nuclear DNA and mtDNA would result in a viable stem like cells capable of propagation and uses in methods of implantation.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

US 2002/0090722 A1 Dominko *et al.* disclose methods of nuclear transfer and specifically disclose the addition of mitochondria (see claim 25 for example). However the earliest effective filing date is June 15, 2000, after the filing date of the instant application.

### ***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (571) 272-0734.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach

A handwritten signature in cursive script that reads "Joe Woitach".

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